PATHOLOGICAL REPORT ON THE EYES OF DR. HIRSCH'S PATIENT WITH AMAUROTIC FAMILY IDIOCY.[1]

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The upper diagram in Chart A represents roughly the ophthalmoscopic picture characteristic of amaurotic family idiocy, and the lower diagram represents a corresponding section of the posterior part of the eyeball passing through the optic disc and macula lutea. In these cases the macular region is occupied by an oval, gray patch about twice as broad as the optic disc, and having a red spot in its centre. In nearly 30 cases that have been reported the eye changes have been remarkably uniform.

As regards the explanation of this fundus picture, which has often been compared to the change following embolism of the central artery of the retina, clinicians have been inclined to believe it to be due to a retinal œdema, rendering the retina opaque, and obscuring the normal red color of the choroid, except in the fovea centralis, where the retina is very thin. This view was taken also by Treacher Collins, the former pathologist of Moorfields, who made a miscroscopic examination of the eyes of two patients. He reported that there was a spacing out of the tissues in the outer reticular layer, indicative of œdema, and no apparent changes in the other layers. But he regarded his examinations as unsatisfactory, since in all the eyes examined the retina about the macula was thrown up into a fold, a common postmortem change. The retinal elements in such folds are always spaced out, so that a deceptive appearance of œdema is presented even in healthy eyes. The fact that Collins noticed no changes in the ganglion cells is not surprising, since little attention is given to the retinal ganglion cells, as a rule, and scarcely any attempts have been made to study them by modern cytological methods.

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The eyes on which I wish to report were removed by Dr. Hirsch four hours after death, and were hardened, one in Müller's fluid and one in formol, 10 per cent. In the formol eye the retina remained in position at the macula, and, after hardening, the gray patch at the macula was seen as in life. Horizontal and vertical sections were cut through the maculas, and longitudinal and transverse sections through the nerves, after celloidin and paraffin imbedding, and every applicable stain was used. The findings were checked in every possible way by comparison with other eyes, in order to rule out errors of interpreta-

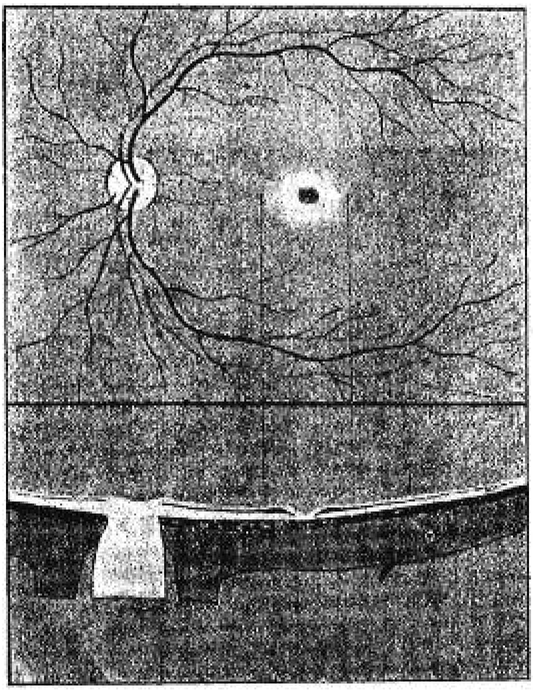

CHART A.

Upper diagram representing the fundus picture; lower diagram representing a corresponding section of the eyeball; the dark line in the retina indicating the layer of ganglion cells.

tion. The eyes of an infant dead of the same disease, pneumonia, were prepared in exactly the same way, and cellular alterations due to postmortem changes, strong hardening solutions, and various general diseases were studied at great length. The work was done in the Pathological Institute of the New York State Hospitals.

In the normal retina the ganglion cells vary from 10 to 30 microns in diameter, and in the periphery of the retina where the cells are scattered, large cells abound, but in the macular region, where the ganglion cell layer is several cells deep, the cells are mostly small, irregularly pear-shaped, and packed close together.

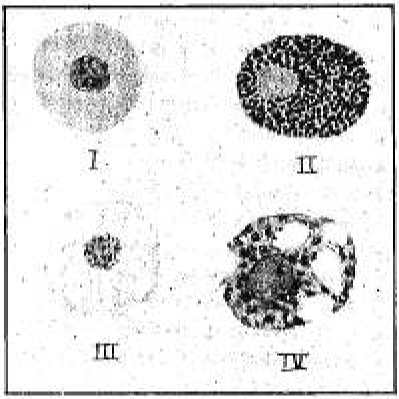

CHART B.

Fig. I. A retinal ganglion cell stained with hæmatoxylin-eosin. Fig. II. The same with Weigert's hæmatoxylin. Fig. III. The same stained by Nissl's method. Fig. IV. A retinal ganglion cell from Dr. Peterson's case stained by Nissl's method.

Sections of the Müller's fluid eye stained with hæmatoxylin-eosin showed the average size of the ganglion cells to be increased and the average shape to be altered toward the globular. (Fig. I., Chart B.) The nuclei were mostly near the centre of the cells. The cell body with this stain appeared homogeneous, but when similar sections were stained by Weigert's method or with hematëin the entire body of the cells appeared to be filled with coarse, black granules. (See Fig. II.)

In Nissl preparations of the formol eye, at first glance, nothing was seen of the ganglion cells but their nuclei, which stained deeply and were coarsely granular. (Fig. III.) Under a 1-18 immersion the cell membrane and the cyto-reticulum could be clearly made out, but no Nissl granules were present, and the cell body had the appearance of having had its liquid contents withdrawn, leaving the naked cell framework. (Fig. III.) These staining reactions characterize the cell absolutely.

Furthermore, comparison with Dr. van Gieson's hematëin preparations of the brain of Dr. Sachs' patient, which was hardened in Müller's fluid, and comparison with Dr. Hirsch's Nissl preparations of the brain of his patient, hardened in formol, showed that the staining reactions in the cerebral and the retinal cells in each case, allowing for their difference in size, were identical. In the eyes of Dr. Peterson's patient, who died at seven months of age, the autopsy being made forty hours after death, postmortem vacuolation was found in the ganglion cells (Fig. IV.), but the nuclei were not granular, and the nucleoli were distinct, while Nissl granules were present in the cell bodies; the advanced changes found in both nuclei and cell bodies in Dr. Hirsch's patient were here wanting.

No actual œdema of the retina was found on careful comparisons with preparations of normal eyes cut in the same directions and thicknesses. The other layers of the retina were apparently normal, excepting the rods and cones, which in their outer segments had undergone the usual early postmortem change. The ciliary nerves were normal, and no ganglion cells giving these peculiar staining reactions were found in the ciliary body.

The optic nerve showed an absence of the myelin in many fibres in each bundle, and the neuroglia tissue was increased—in other words, the condition was that of simple degeneration.

The changes in the ganglion cells readily explain the fundus picture, which, indeed, admits no other anatomical explanation.

In the fovea centralis ganglion cells are practically absent. At the margins of the fovea the ganglion-cell layer abruptly increases in thickness, until it is from 6 to 10 cells deep. A disc diameter from the fovea, horizontally in either direction, the ganglion-cell layer has thinned down to a layer from 3 to 4 cells deep; two disc diameters from the fovea it is from 2 to 3 cells deep, and beyond this it thins down further to a layer from 1 to 2 cells deep, while in the periphery of the retina it is a single broken layer of scattered cells (see diagram, Chart A). Above and below the fovea centralis, in the vertical meridian, the ganglion-cell layer thins out rather more rapidly than in the horizontal meridian. The oval gray patch occupies, therefore, exactly that portion of the retina in which the layer of enlarged and altered ganglion cells is four or more cells deep. At the margins of the patch, where the ganglion-cell layer is thinner, the faint gray color fades away gradually into the normal red of the fundus. Near the fovea centralis, where the ganglion-cell layer is thickest, the gray color is most intense, and in the fovea centralis, where ganglion cells are wanting, the red color of the choroid shows through, appearing darker by reason of contrast with the surrounding light gray.

Tay, who first described this disease, and also Kingdon have followed the course of the fundus changes. They have found that the fundus is normal until after the third month. Then a haziness appears in the macular region, and the usual picture is fully developed in the fifth or sixth month. At this time the infant often has enough vision to follow a light. A month or two later, the macular picture remaining the same, vision is lost, and the optic nerve becomes atrophic. Although the macula lutea is not fully differentiated at birth, its layer of ganglion cells is five or six cells deep, and the fact that the retina is then ophthalmoscopically transparent indicates that the ganglion cells cannot be much affected, if at all. The optic nerve atrophy which follows the appearance of the macular changes is to be interpreted, perhaps, as both an ascending and a descending degeneration—a breaking down of the neuraxons of the affected retinal ganglion cells and of the affected ganglion cells in the basal ganglia.

We have thus found a common explanation for the symptoms of this complex affection, and have shown it to be pathologically a unit. The ocular neurons have undergone a primary alteration, like the cerebral neurons. Nor should this cause surprise, when we remember that the retina and the optic nerve are genetically a portion of the brain, being developed embryologically from the same medullary tube of involuted ectoderm. Embryologically related to the brain, the inner layers of the developed retina are so similar in histological structure to the cerebral cortex that they are known as the cerebral stratum of the retina. Analogous, embryologically and histologically, we have seen also that the retina and cortex may suffer analogous primary pathological changes. And in future investigations of nervous diseases, we must consider the retina a division of the central nervous system, which is quite as worthy of study by the pathologist as are the brain and cord.

DISCUSSION.

Dr. B. Sachs said that it was a great satisfaction to him that a paper read by him on this subject before the association, eleven years ago, had led to so interesting a discussion. He was firmly convinced that amaurotic family idiocy was a morbid entity, which he knew would be placed upon a firmer basis by the extensive pathological studies made by Drs. Hirsch, Holden and Peterson. The speaker said that when he first entered upon the study of this special disease, he had no theory in mind as regarded its causation, and even to this day he had not formulated any theory, nor did he think that the time for such a formulation had arrived.

Dr. Sachs stated that considerable emphasis had been placed upon the circumstance that a disease which was supposed to be a congenital one did not apparently develop its symptoms until four or five months after birth. His answer to that statement was that the latter fact did not prove that the disease was not congenital, because it was extremely difficult to prove that a child under the age mentioned was perfectly normal in every respect. Moreover, in a case which had been under his observation, he had been able to satisfy himself that the child, when only three months old, was mentally deficient. The statement of the mother in regard to the mental condition of the child at a very early age was not always conclusive. As these patients grow older, both the mental and physical deterioration become more marked, and many of them die in a condition of marasmus. This last fact he wished especially to emphasize.

As regards the seat of the lesions in these cases, the speaker said that Dr. Hirsch had done excellent work in showing that the disease is not restricted merely to the brain or cerebral cortex, but may affect the entire nervous system, including even the cells in the gray matter of the cord. The cellular changes are similar throughout the central nervous system, and the pathological findings of Dr. Hirsch were entirely in accord with those in two cases of his own, one examined eleven and the other nine years ago. The speaker said that in his earlier researches on this subject he had interpreted the disease as being chiefly cortical in origin, but even at that time he had a suspicion that the lesions were not confined to the cortex, and Dr. H. Knapp, who had examined the eyes in his first case, insisted at the time that it would some day be found that the changes in the optic nerves were parallel to the changes in the cortex. In Dr. Sachs' second case the changes were present in the brain and spinal cord; the changes in the latter region he at first ascribed to secondary degeneration, but later on he came to the conclusion that they were the result of arrested development. Kingdon and Russell, on the other hand, were the first to claim that the changes were due to degeneration. Dr. Sachs was of the opinion that an arrest of development is necessarily followed by a degeneration, and for that reason he did not think there was such a radical difference between the interpretation put upon the cases by Kingdon and Russell, and now by Dr. Hirsch, and that of himself.

With regard to the cause of this degenerative process, Dr. Sachs said that, while the theory advanced by Dr. Hirsch was very interesting, it was probably influenced to some extent by the theory of another illustrious author, who had attempted to explain hereditary influence on the basis of a toxic infection. The speaker said he could not believe that a disease so widespread as this, which begins at the same period of life, and which involves several members of the same family and leaves others exempt, could be due to any toxic influence that is known to us. As an argument against the theory that the disease was carried through the mother's milk, the speaker cited his first two cases, who, although Jewish children, were not raised on mother's milk.

Dr. Sachs said that, personally, he had no theory to offer regarding the causation of this disease. He thought it was in line with many of the hereditary diseases, and we must accept it as a hereditary family disease of the central nervous system. It certainly bears a close clinical relationship to other hereditary family affections, particularly to those characterized by blindness, for example, or to those characterized by spastic paraplegia and forms of mental defect.

The evidence furnished by Dr. Hirsch of involvement of the gray matter of the spinal cord explains why in some cases the paralysis is spastic and in others flaccid (as in Sachs' first patient). In conclusion, Dr. Sachs said that, while he regarded this as a widespread disease of the central nervous system, he did not believe that the spinal cord need always be affected, and that in some instances the disease may be chiefly cerebral.

Dr. Carl Koller had seen five cases of this interesting affection. Two cases, which he had published a few years ago in a paper read before the American Ophthalmological Society, had been the immediate occasion of this question being taken up again by Dr. Sachs. A number of cases had been reported in quick succession, and a thorough study made of it clinically by Dr. Sachs, and later, pathologically, by Dr. Hirsch, whose painstaking and exhaustive research had greatly contributed to our understanding of the disease.

Dr. Koller said that the characteristic ophthalmoscopic changes in the macula were not congenital, and were not found until between the fifth and seventh months. In two of Kingdon's cases, which were examined in the earlier months of life, they were missing, and in two cases of the speaker, which were examined in the first two months of life, they were also absent. One of the latter was the identical case which Dr. Peterson had just reported in his paper. The speaker said he had examined that child five times between the eighth and sixteenth weeks of its life, the ophthalmoscopic examination being negative, although other unmistakable signs were present which proved that the case belonged to this class. In the other case, the characteristic changes developed later.

Dr. Koller thought that the atrophy of the optic nerve in these cases made its appearance considerably later than the changes in the macula, and developed gradually. As to whether the former depends on the latter, or whether one was independent of the other, that point remained for pathologists to determine, but it seemed reasonably certain that, as a rule, the ocular changes were not congenital.

Another question arising in connection with this subject was whether these patients ever had sight, in our meaning of the word; whether they were born blind, or with a vision already impaired by existing cerebral changes; or whether they were born with a vision equal to the low degree pertaining to the newborn, with degeneration setting in before the vision became developed to a higher plane. At all events, the behavior of the children with regard to their vision was not normal at the time when no ophthalmoscopic changes were visible, and the conclusion was permissible that vision was impaired by cerebral degeneration lying pretty far back. In one of the speaker's cases the mother had her suspicions in regard to the child's eyesight as early as the fourth week of life. In the two cases he had examined in the 8th and 9th weeks he had received the impression that vision was already impaired. The light of a candle in a dark room was not followed by the eyes, and no prompt reaction of the pupils could be produced. The pupils became slowly narrower when exposed to light, and slowly dilated in the dark. The speaker thought these two facts certainly deserved weight, considering the difficulty which exists as to how much vision such young children enjoy.

Dr. Charles K. Mills concurred with Dr. Sachs in regard to the nature of amaurotic family idiocy. The word "congenital" in connection with these cases seemed to him to be sometimes misused. In many of these cases the clinical, and, possibly, the pathological, evidences of the disease, so far as can be demonstrated, are not observed until weeks, months, years, or even decades, after the birth of the individual, and in this sense they are not congenital; but these cases, along with some of the forms of diplegia and of muscular atrophy, and perhaps of Huntington's chorea and developmental insanities, belong to a great embryonal class. The potentiality of development in these cases is limited, and it may be weeks, months or years before the symptoms make their appearance. Whether the immediate pathological conditions which initiate the manifestations of the disease are toxic or non-toxic, sooner or later the degenerative process will manifest itself, if the individual survives long enough.

Dr. F. X. Dercum said that he had reported one family in which three of the four children suffered from spasmodic diplegia and idiocy. Sachs, Freud, and others had reported similar instances. In his three cases the symptoms of the degenerative process manifested themselves in each instance immediately after measles; the only child that escaped did not contract measles. Such observations as these, Dr. Dercum thought, tended to strengthen the toxic theory of amaurotic family idiocy.

Dr. W. G. Spiller reported the case of a child, born of healthy parents, but who had an aunt insane and an uncle who was feeble-minded. The child had presented no symptoms detectable by the parents until he went to school, when he was noticed to be somewhat feeble mentally. His gait and speech were rather slow; he lisped slightly, and his circulation was imperfect. As time went on, spastic symptoms developed, and gradually became very marked; the reflexes were much exaggerated, intention tremor was noticed, the speech became scanning, and was finally lost. The later developments were incoördination, feeble mentality, muscular contractures, intense atrophy, and finally complete paralysis. When the boy was thirteen years old, bilateral optic atrophy was noted, but it may have existed for some years before the examination was made. The child died at the age of fifteen. A microscopical examination showed distinct degeneration of the pyramidal tracts of the cord. The cells of the anterior horns and the spinal roots appeared to be little altered. The brain could not be obtained.

Dr. Spiller said he did not consider this case a typical one of amaurotic family idiocy, and yet it bore certain resemblances to this disease. It seemed to him to have a closer relation to the pseudo-sclerosis of Westphal and Strümpell, for the pyramidal tracts were not normal in all instances. As only five cases of this pseudo-sclerosis are now on record, Dr. Spiller was inclined to regard his case as a sixth. The report will be published in detail later.

Dr. Hirsch, in closing, said he did not think we could dispense with the distinction between a disturbance of development and an acquired disease. To accept the statement that an arrest of development is identical with an acquired disease would mean to destroy wilfully the most valuable scientific work of the last decades. In the nervous system, as elsewhere in the body, a certain predisposition to disease may be inherited; tuberculosis, for example, although a strong predisposition to it may be inherited, cannot develop without the presence of the tubercle bacilli. The speaker said he did not question the fact that children who develop amaurotic family idiocy were born with a normal nervous system. If the changes in the macula lutea are produced by changes in the ganglion cells, we must assume that as long as the former changes are absent the ganglion cells are normal, and it is to-day a clinically established fact that the children are not born with the peculiar condition in the macula lutea, but that this develops during the course of the disease. In his case the optic tract was atrophied; this atrophy was secondary; it was an acquired condition; the child was not born with it, but had impaired vision up to the age of eight months.

Dr. Hirsch said he agreed with the previous speakers that the toxic origin of this disease was still an open question. As regards the milk theory, he did not think it was disproven by the instance cited by Dr. Sachs, where two Jewish children, who afterward developed the disease, had been brought up by Christian wet-nurses. From the fact that all the cases which have been observed so far belonged to the Jewish race, it does not follow that the toxin must also necessarily be of Jewish origin.

The speaker said he wished to take exception to the statement that amaurotic family idiocy was in line with other hereditary diseases. He knew of no other inherited family disease where all the nerve cells, and nothing but the nerve cells, in the body became affected; the condition, so far as he knew, had no analogy in pathology. Furthermore, in this disease the degenerated cells had a typical appearance, only analogous to what we see in poisoning, and that, in spite of this, they had certain characteristics of their own, was in accordance with the modern view that every poison had a specific action on nerve cells.

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167. DELIRE DE PERSECUTION; KYSTE DERMOIDE DE L'OVAIRE; LAPAROTOMIE; DISPARITION DES TROUBLES MENTAUX (Delirium of Persecution; Dermoid Cyst of the Ovary; Laparotomy; Cessation of the Mental Trouble). A. Voisin (La France Méd. et Paris Méd., Feb. 12th, '97).

Under this title the author publishes the following case: The patient, with a neuropathic family history, had a pessary introduced for prolapsis uteri, six years ago. Being a virgin, this treatment made such an impression on her as to disturb her mental faculties, and she became sad and at times showed violent temper. Later on she developed marked delirium of persecution, with hallucinations of sight and hearing, accused several persons of plotting against her, and tried to commit suicide twice. In November last, laparotomy was performed, and a large multilocular ovarian cyst extracted. For two days after the operation the patient was somewhat excited, then all the cerebral disturbances ceased permanently. The foregoing observations of mental disturbance, being cured by a surgical operation, is considered as extremely rare and interesting, inasmuch as one is accustomed to observe mental symptoms develop subsequent to surgical interference upon the female genital organs. MACALESTER.